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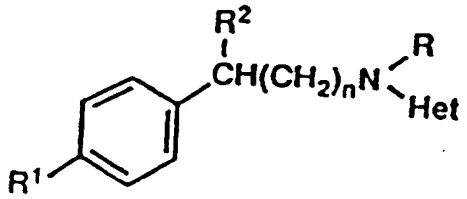

(I)

(57) Abstract

Compounds of formula (I), wherein R is C_1-C_4 alkyl; R^1 is R^3SO_2NH or R^3CONH; R^2 is H or OH; R^3 is C_1-C_4 alkyl, C_3-C_7 cycloalkyl or NR^4R^5; R^4 and R^5 are each independently selected from H and C_1-C_4 alkyl; "Het" is either (a) 2-, 3- or 4-pyridyl optionally substituted by one or two substituents each independently selected from NH_2 and C_1-C_4 alkyl, or (b) 2-imidazolyl optionally substituted by one or two C_1-C_4 alkyl groups; and n is 1, 2, or 3; and pharmaceutically acceptable salts thereof, are antiarrhythmic agents.

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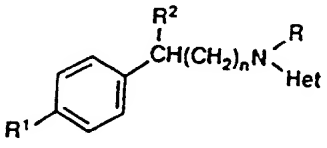
"ANTIARRHYTHMIC AGENTS"

This invention relates to antiarrhythmic agents useful in the treatment of cardiac arrhythmias.

The compounds of the invention prolong the duration of the action potential in cardiac muscle and conducting tissue, and thereby increase refractoriness to premature stimuli. Thus, they are Class III antiarrhythmic agents according to the classification of Vaughan Williams (Antiarrhythmic Action, E. M. Vaughan Williams, Academic Press, 1980). They are effective in atria, ventricles and conducting tissue both in vitro and in vivo and are therefore useful for the prevention and treatment of a wide variety of ventricular and supraventricular arrhythmias including atrial and ventricular fibrillation. Because they do not alter the speed at which impulses are conducted, they have less propensity than current drugs (mostly Class I) to precipitate or aggravate arrhythmias, and they also produce fewer neurological side effects. Some of the compounds also have positive inotropic activity and therefore are particularly beneficial in patients with impaired cardiac pump function.

The invention provides compounds of the formula:



(I)

and their pharmaceutically acceptable salts,

wherein R is C_1-C_4 alkyl;

R^1 is R^3SO_2NH or R^3CONH,

wherein R^3 is C_1-C_4 alkyl, C_3-C_7 cycloalkyl or NR^4R^5,

wherein R^4 and R^5 are each independently selected from H and C_1-C_4 alkyl;

R^2 is H or OH;

"Het" is either (a) 2-, 3- or 4-pyridyl optionally substituted by 1 or 2 substituents each independently selected from NH_2 and C_1-C_4 alkyl, or (b) 2-imidazolyl optionally substituted by 1 or 2 C_1-C_4 alkyl groups;

and n is 1, 2 or 3;

In the above definition, C_3 and C_4 alkyl groups may be straight or branched chain.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as enantiomers or diastereoisomers. The invention includes both mixtures and separate individual isomers.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts formed from pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, maleate, fumarate, succinate, lactate, citrate, tartrate, gluconate, benzoate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

Some of the compounds, e.g. those wherein R^1 is R^3SO_2NH, may also form metal salts, particularly alkali metal and alkaline

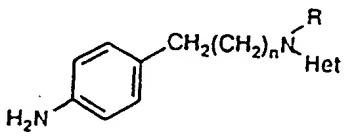
earth salts. Examples of the former include the sodium and potassium salts.

A preferred group of compounds of the formula (I) is that wherein R^1 is R^3SO_2NH; R^3 is C_1-C_4 alkyl or $NH(C_1$-C_4 alkyl); "Het" is either (a) 2- or 4-pyridyl optionally substituted by NH_2, or (b) 1-(C_1-C_4 alkyl)-2-imidazolyl optionally further substituted by a C_1-C_4 alkyl group; and n is 1.

A particularly preferred group of compounds of the formula (I) is that wherein R is methyl; R^1 is CH_3SO_2NH or CH_3NHSO_2NH; "Het" is either (a) 4-amino-2-pyridyl or 4-pyridyl, or (b) 1-methyl-2-imidazolyl or 1,5-dimethyl-2-imidazolyl; and n is 1.

The compounds of the formula (I) provided by the invention may be prepared by the following methods.

(1) Compounds of the formula (I)$_a$, wherein "Het" is either (a) 2-, 3- or 4-pyridyl optionally substituted by 1 or 2 C_1-C_4 alkyl groups, or (b) 1-(C_1-C_4 alkyl)-2-imidazolyl optionally further substituted by a C_1-C_4 alkyl group, R^2 is H, and R, R^1 and n are as defined for formula (I), may be prepared from intermediates of the formula:



(II)

wherein "Het" is as defined in this method and R and n are as defined for formula (I).

The compounds of the formula (I), wherein "Het", R and n are as defined for formula (II) and R^1 is

a) R^3SO_2NH,

wherein R^3 is C_1-C_4 alkyl, C_3-C_7 cycloalkyl or NR^4R^5, wherein R^4 is H or C_1-C_4 alkyl and R^5 is C_1-C_4 alkyl, can be prepared by reacting a compound of the formula (II) with a sulphonyl halide of the formula (C_1-C_4 alkyl or C_3-C_7 cycloalkyl)SO_2(Cl or Br), a sulphonic anhydride of the formula [(C_1-C_4 alkyl or C_3-C_7 cycloalkyl)SO_2]$_2$O or with a sulphamoyl chloride of the formula $R^4R^5NSO_2Cl$, wherein R^4 is H or C_1-C_4 alkyl and R^5 is C_1-C_4 alkyl, in the presence of a suitable acid acceptor, e.g. triethylamine or pyridine. The reaction is typically carried out at from 0°C to room temperature in a suitable organic solvent, e.g. dichloromethane. Preferably, the reaction is carried out using pyridine as both the solvent and the acid acceptor;

b) H_2NSO_2NH,

can be prepared by reacting a compound of the formula (II) with sulphamide at up to, and preferably at, the reflux temperature in a suitable organic solvent, e.g. 1,4-dioxane;

c) R^3CONH,

wherein R^3 is C_1-C_4 alkyl or C_3-C_7 cycloalkyl, can be prepared by acylating a compound of the formula (II) with either an acid halide of the formula (C_1-C_4 alkyl or C_3-C_7 cycloalkyl)CO(Cl or Br) or with an acid anhydride of the formula [(C_1-C_4 alkyl or

C_3-C_7 cycloalkyl)CO]$_2$O. When an acid halide is employed the reaction is typically carried out at from 0°C to room temperature in a suitable organic solvent, e.g. dichlorormethane, and in the presence of a suitable acid acceptor, e.g. triethylamine or pyridine. The reaction may also be carried out using pyridine as both the solvent and the acid acceptor. When an acid anhydride is employed the reaction is typically carried out at up to the reflux temperature, preferably at 100°C, in a suitably compatible organic solvent, e.g. a carboxylic acid of the formula (C_1-C_4 alkyl or C_3-C_7 cycloalkyl)COOH;

d) H_2NCONH-

can be prepared by reacting a compound of the formula (II) with sodium or potassium cyanate at up to, and preferably at, the reflux temperature in a suitable acidic solvent medium, e.g. aqueous acetic acid;

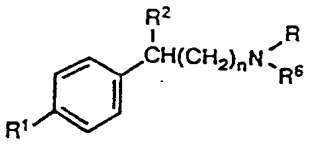
e) (C_1-C_4 alkyl)NHCONH,

can be prepared by reacting a compound of the formula (II) with a (C_1-C_4 alkyl) isocyanate. The reaction is preferably carried out at room temperature in a suitable organic solvent, e.g. dimethylformamide although, if necessary, elevated temperatures may be employed to accelerate the rate of reaction;

or f) (C_1-C_4 alkyl)$_2$NCONH,

can be prepared by reacting a compound of the formula (II) with a carbamoyl chloride of the formula $(C_1-C_4$ alkyl$)_2NCOCl$. The reaction is typically carried out at from 0^oC to the reflux temperature in a suitable organic solvent, e.g. dichloromethane, and in the presence of a suitable acid acceptor, e.g. triethylamine or pyridine.

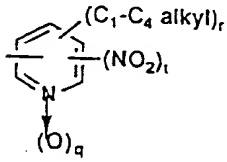
(2) Compounds of the formula (I), wherein "Het", R, R^1, R^2 and n are as defined for formula (I), may be prepared from intermediates of the formula:



(III)

wherein R, R^1, R^2 and n are as defined for formula (I) and R^6 is either H (IIIA)

or

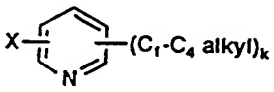


(IIIB)

wherein q is 0 or 1, r is 0 or 1 and t is 1 or 2, with the proviso that the sum of r and t is 1 or 2.

The compounds of the formula (I), wherein R, R^1, R^2 and n are as defined for formula (I) and "Het" is

a) 2- or 4-pyridyl optionally substituted by 1 or 2 C_1-C_4 alkyl groups, may be prepared by reacting a compound of the formula (IIIA) with a halopyridine of the formula:



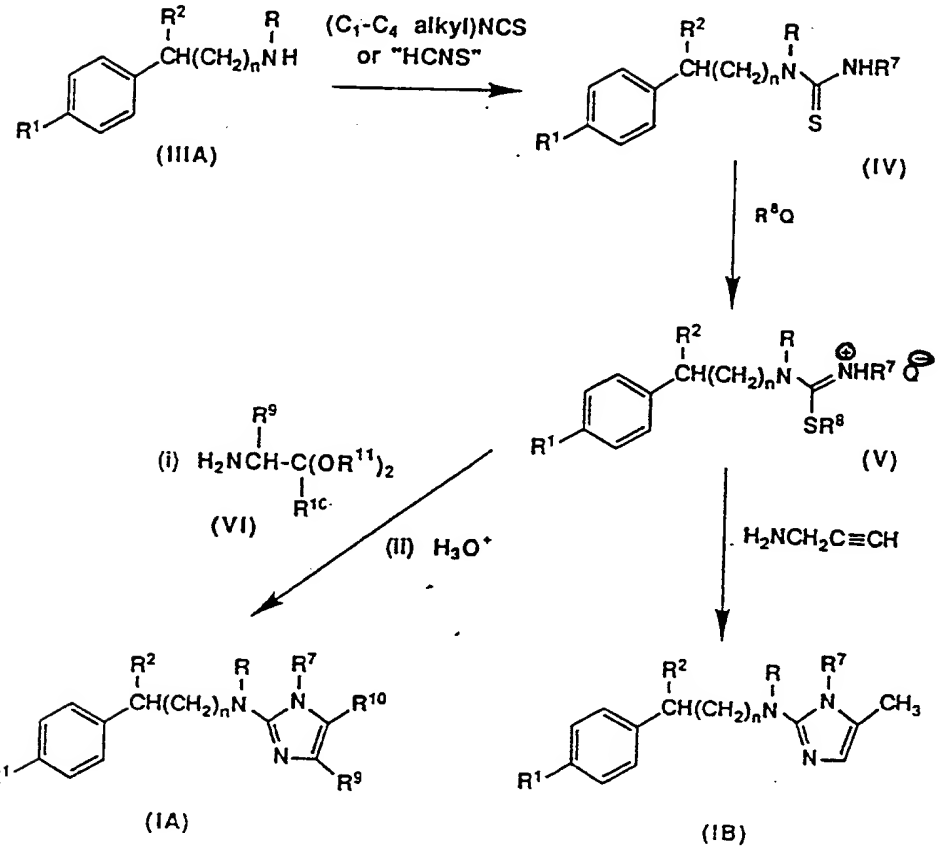
wherein X is 2- or 4- halo, preferably Cl or Br, and k is 0, 1 or 2. The reaction is typically carried out at up to, and preferably at, the reflux temperature in a suitable organic solvent, e.g. n-butanol or amyl alcohol, and in the presence of a suitable acid acceptor, e.g. sodium carbonate or sodium bicarbonate;

b) 2-, 3- or 4- pyridyl substituted by 1 NH_2 group and optionally further substituted by 1 NH_2 group or by 1 C_1-C_4 alkyl group, can be prepared by reduction of a compound of the formula (IIIB) using conventional methods. Preferably, the reduction is carried out by catalytic hydrogenation using a suitable catalyst, e.g. palladium on charcoal, at room temperature and in a suitable inert organic solvent, e.g. ethanol;

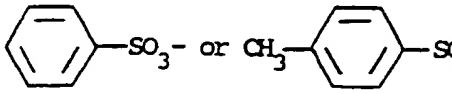
or c) 2-imidazolyl optionally substituted by 1 or 2 C_1-C_4 alkyl groups, can be prepared from a compound of the formula

(IIIA), e.g. as described in Preparation 4 of the Preparations section, according to Scheme 1:

Scheme 1



wherein R^7 is H or C_1-C_4 alkyl, R^8 is C_1-C_4 alkyl, R^9 and R^{10} are each independently H or C_1-C_4 alkyl, each R^{11} is C_1-C_4 alkyl or the two groups R^{11} are joined to form a C_2-C_3 alkylene chain, and Q is preferably halo (preferably iodo), (C_1-C_4 alkyl)SO_3-,



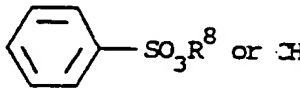
-SO_3- or

-SO_3-; with the proviso that not more than two of R^7, R^9 and R^{10} in formula (IA) are C_1-C_4 alkyl.

In the first step, a compound of the formula (IIIA) is either (a) reacted with a C_1-C_4 alkyl isothiocyanate in a suitable organic solvent, e.g. methanol or dichloromethane, at about room temperature to give a thiourea of the formula (IV) wherein R^7 is C_1-C_4 alkyl, or (b) reacted with a thiocyanate salt, e.g. ammonium, sodium or potassium thiocyanate, under acidic conditions to give a thiourea of the formula (IV) wherein R^7 is H.

The thiourea (IV) is then S-alkylated, preferably using a C_1-C_4 alkyl halide (preferably an iodide) or a compound of the formula

(C_1-C_4 alkyl)SO_3R^8,



-SO_3R^8 or

-SO_3R^8.

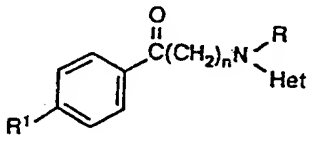
The S-alkyl derivative (V) can then be converted to an imidazole by two different methods.

In the first method, the S-alkyl derivative (V) is reacted with the acetal or ketal (VI), e.g. by heating at from 60-130°C and preferably under reflux in a suitable organic solvent (such as pyridine), to form an intermediate guanidine. The guanidine is then heated in aqueous acid, e.g. aqueous hydrochloric acid, and

preferably under reflux, to cyclise it to the product (IA).

In the second method, the S-alkyl derivative (V) is converted to the imidazole (IB) by reaction with propargylamine in a suitable organic solvent, e.g. pyridine, typically at a temperature of from 60-130°C and preferably under reflux.

(3) Compounds of the formula (I), wherein R^2 is OH, and R, R^1, "Het" and n are as defined for formula (I), may be prepared from intermediates of the formula:



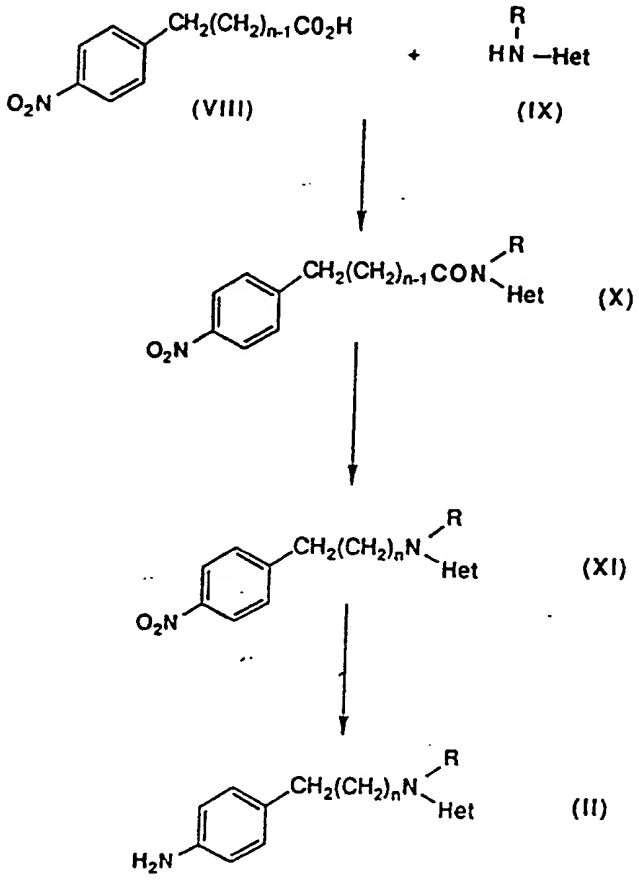
(VII)

wherein R, R^1, "Het" and n are as defined for formula (I), by reaction of (VII) with a reducing agent such as sodium borohydride. The reduction is typically carried out in a suitable solvent, e.g. aqueous ethanol, at from 0°C to reflux temperature.

The intermediates of the formulae (II), (IIIA), (IIIB) and (VII), required for the preparation of the compounds of the invention of the formula (I), may be prepared by the following methods.

(i) The intermediates of the formula (II), wherein "Het", R and n are as previously defined for formula (II), can be prepared by conventional techniques, e.g. as described in Preparation 1 of the Preparations section and as summarised in Scheme 2:

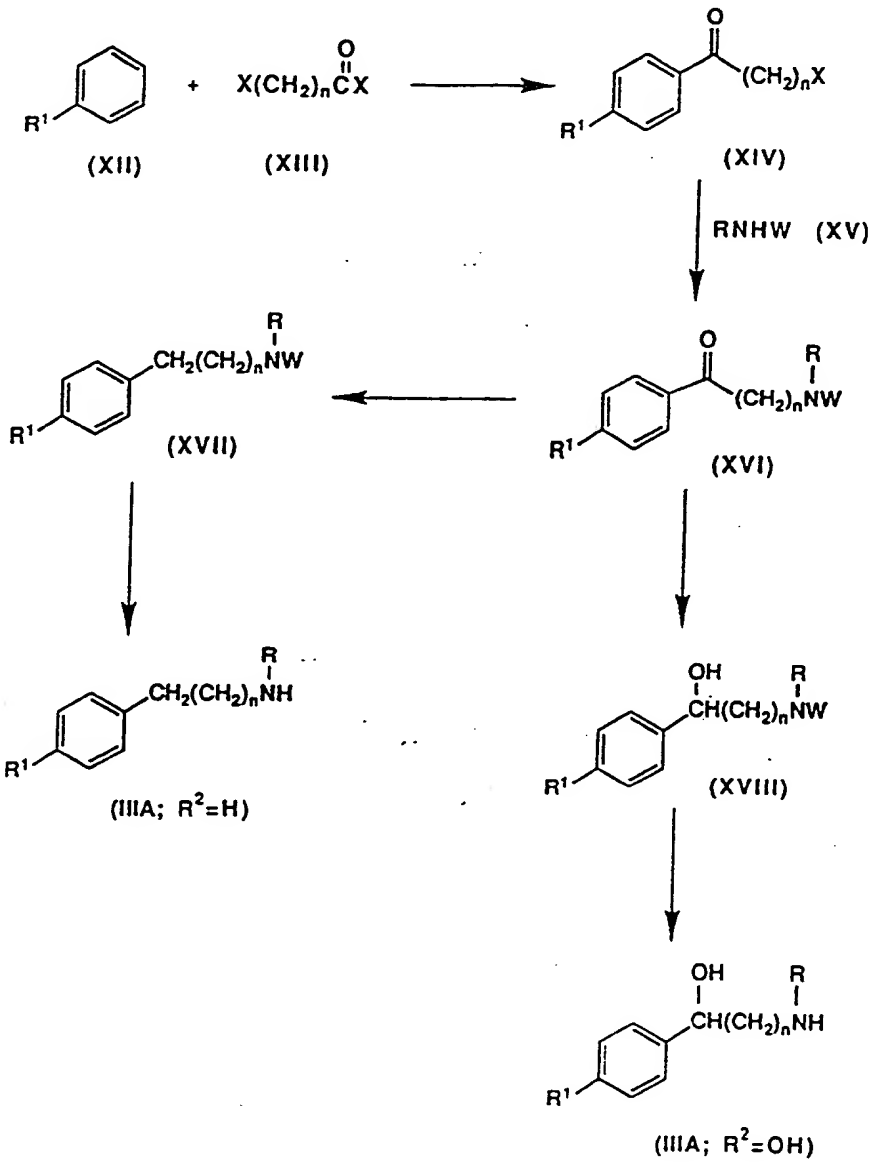
Scheme 2


CH2(CH2)n-1CO2H
O2N
(VIII)
R
HN—Het
(IX)
CH2(CH2)n-1CON
Het
(X)
CH2(CH2)nN
Het
(XI)
H2N
(II)

In the first step, a carboxylic acid of formula (VIII) is coupled with an amine of formula (IX) to afford an amide of formula (X). This may be effected by prior activation of (VIII), using a conventional peptide coupling reagent such as N,N'-dicyclohexylcarbodiimide, or by prior formation of the corresponding acyl halide, e.g. the acyl chloride, using a conventional chlorinating reagent such as thionyl chloride. In the latter case, the coupling is preferably carried out in the presence of an excess of a suitable acid acceptor, e.g. triethylamine. Conversion of the amide (X) to amine (XI), in the second step, can be achieved by use of a typical amide reducing agent such as diborane whilst, in the third step, the nitro group of (XI) may be reduced, for example, by catalytic hydrogenation using a palladium catalyst, to provide the intermediate (II).

(ii) The intermediates of the formula (IIIA), wherein R, R^1, R^2 and n are as previously defined for formula (III), can be prepared by conventional techniques such as those summarised in Scheme 3:

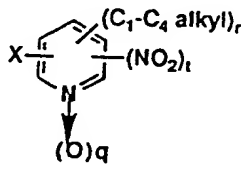
Scheme 3



wherein W is a suitable amine protecting group such as benzyl, and X is a halogen atom, preferably chlorine or bromine.

In the first step an appropriate arene of formula (XII), wherein R^1 is as previously defined for the formula (I), is acylated with an ω-haloacyl halide of formula (XIII) under typical Friedel-Crafts conditions, e.g. in the presence of aluminium chloride, to afford an ω-haloketone of formula (XIV) which, in the second step, is used to alkylate a protected amine of the formula (XV) wherein R is as previously defined for the formula (I). The said alkylation is preferably conducted in the presence of an excess of a suitable acid acceptor, e.g. triethylamine, to furnish the ω-aminoketone of formula (XVI). The latter may then be either fully reduced to the ω-aminoalkane of formula (XVII) or partially reduced to the ω-aminoalcohol of formula (XVIII). The former reduction may be carried out by classical procedures such as the Clemmensen or Wolff-Kishner reductions, whilst reduction of the ketone to the corresponding alcohol may be effected with sodium borohydride. Subsequent removal of the protecting group from either (XVII) or (XVIII) in the final steps may be achieved, for example, by catalytic hydrogenolysis using a palladium catalyst, to afford intermediates of the formula (IIIA) wherein R^2 is H or OH respectively.

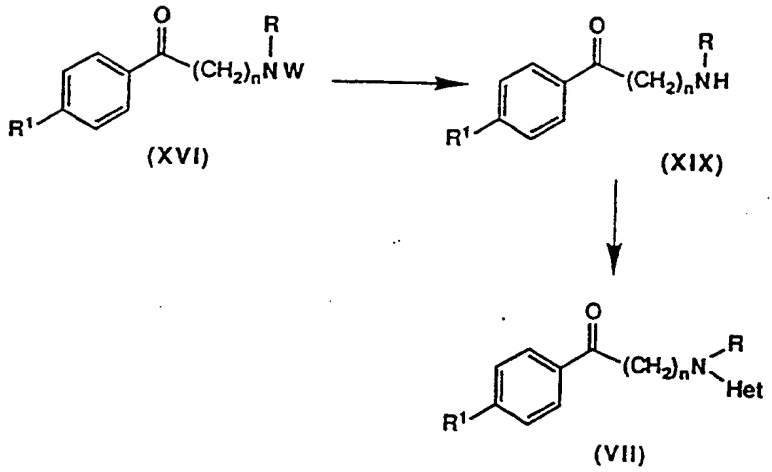
(iii) The intermediates of the formula (IIIB), wherein R, R^1, R^2, n, q, r and t are as previously defined for formula (IIIB), can be prepared by conventional techniques, e.g. as described in Preparations 2 and 3 of the Preparations section, by reacting a compound of the formula (IIIA) with a halopyridine of the formula:



wherein X is a halogen atom, preferably Cl or Br, and q, r and t are as previously defined for the formula (IIIB). The reaction is typically carried out in the presence of an excess of a suitable acid acceptor, e.g. pyridine, which may also serve as an appropriate solvent.

(iv) The intermediates of the formula (VII), wherein "Het", R, R^1 and n are as previously defined for formula (VII), can be prepared by conventional techniques such as those summarised in Scheme 4:

Scheme 4



wherein W is as previously defined in Scheme 3.

The intermediate of formula (XVI), which may be synthesised as described within Scheme 3, can be deprotected as described for the analogous deprotections of the compounds of formulae (XVII) and (XVIII), in Scheme 3, to provide the ω-aminoketone of formula (XIX). Conversion of (XIX) to intermediates of formula (VII) may then be effected by the procedures described in Method 2, by analogy with the conversion of intermediates of formula (IIIA) to compounds of the formula (I).

The invention also includes any novel intermediates disclosed herein, such as those of the formulae (II), (III) and (VII).

All of the above reactions are entirely conventional and

appropriate reagents and conditions for their performance, and procedures for isolating the desired products, can readily be established by reference to standard organic chemistry textbooks and to the Examples provided hereafter. Alternatives and variations, in accordance with literature precedent, will also be evident to the person skilled in the art to enable all the compounds defined by formula (I) to be prepared.

Pharmaceutically acceptable salts are readily prepared by mixing solutions containing equimolar amounts of a free base of the formula (I) and the desired acid. The salt is isolated either after its precipitation from solution or after its recovery by evaporation of the solvent employed.

The biological activity of the compounds of the invention is assessed by measuring the effect of the compounds on atrial refractoriness. In this test guinea pig right hemiatria are mounted in a bath containing physiological salt solution, with one end connected to a force transducer. The tissues are stimulated at 1 Hz using field electrodes. Effective refractory period (ERP) is measured by introducing premature stimuli (S_2) after every 8th basic stimulus (S_1). The S_1S_2 coupling interval is gradually increased until S_2 reproducibly elicits a propagated response. This is defined as the ERP. The test compound is then added to the bath and the concentration of compound required to increase ERP by 25% is determined (ED_{25}). ERP is also measured in guinea pig right papillary muscles incubated in physiological saline solution. Muscles are stimulated at one end using bipolar electrodes and the propagated electrogram is recorded at the opposite end *via* a unipolar surface electrode. ERP is determined

as above using the extrastimulus technique. Condition time is obtained from a digital storage oscilloscope by measuring the interval between the stimulus artefact and the peak of the electrogram (i.e. the time required for the impulse to travel along the length of the muscle).

Atrial and ventricular ERPs are also measured in anaesthetised or conscious dogs by the extrastimulus technique whilst the atrium or right ventricle is being paced at a constant rate.

For human use the compounds of the formula (I) can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. They can be administered both to patients suffering from arrhythmias and also, prophylactically, to those likely to develop arrhythmias. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic with blood.

For administration to man in the curative or prophylactic treatment of cardiac conditions such as ventricular and supraventricular arrhythmias, including atrial and ventricular

fibrillation, it is expected that oral dosages of the compounds of the invention will be in the range from 1 to 75 mg daily, taken in up to 4 divided doses per day, for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules might contain 1 to 25 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration would be expected to be within the range 0.5 to 10 mg per single dose as required. A severe cardiac arrhythmia is preferably treated by the i.v. route in order to effect a rapid conversion to the normal rhythm. Variations on these dosages may occur depending on the weight and condition of the subject being treated and will be determined by the medical practitioner.

Thus the present invention provides a pharmaceutical composition comprising a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of preventing or reducing cardiac arrhythmias in a human being, which comprises administering to said human being an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as defined above.

The invention yet further provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament, in particular as an antiarrhythmic agent.

The invention also provides the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or reduction of

cardiac arrhythmias.

The preparation of the compounds of the invention will now be more particularly illustrated by reference to the following experimental Examples. The purity of the compounds was routinely monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F_{254} plates. ^{1}H-Nuclear magnetic resonance spectra were recorded using a Nicolet QE-300 spectrometer and were in all cases consistent with the proposed structures.

EXAMPLE 1

N-[4-[2-[[Methyl(4-pyridyl)]amino]ethyl]phenyl]methanesulphonamide

Methanesulphonyl chloride (0.126 g) was added to a stirred solution of the product of Preparation 1 (0.227 g) in pyridine (2.0 ml) at 0°C. The mixture was stirred for 18 hours, evaporated under vacuum and the residue dissolved in the minimum volume of water. The resulting solution was basified with saturated aqueous sodium bicarbonate solution and the resulting solid was filtered off, washed with water and dried. Purification by chromatography on silica gel, using a 9:1 mixture of dichloromethane and methanol as eluent, gave the product as a solid (0.18 g), m.p. 227-228°C (after crystallisation from ethyl acetate-methanol). Found: C,58.91; H,6.33; N,13.78. $C_{15}H_{19}N_3O_2S$ requires: C,58.99; H,6.27; N,13.76%.

EXAMPLE 2

1-Methyl-3-[4-[2-[[methyl(4-pyridyl)]amino]ethyl]phenyl]sulphamide

Methylsulphamoyl chloride (0.155 g) was added to a stirred solution of 4-amino-N-methyl-N-(4-pyridyl)benzeneethanamine (the product of Preparation 1) (0.227 g) in pyridine (2 ml) and the mixture was stirred for 18 hours at room temperature and then evaporated under vacuum. The residue was treated with a few ml of dilute aqueous ammonia solution and the resulting mixture extracted with ethyl acetate. A small amount of insoluble material was filtered off and the organic layer of the filtrate was separated. The aqueous layer was extracted several times with ethyl acetate and the organic layers were combined, washed with water and dried (Na_2SO_4). Evaporation under vacuum of the solvent

gave a solid which was chromatographed on neutral alumina. Elution with a 20:1 mixture of dichloromethane and methanol, then evaporation under vacuum of the appropriate fractions, gave a gum which crystallised on trituration with ethyl acetate containing a trace of methanol to give the title compound (0.10 g), m.p. 135-137°C (after recrystallisation from ethyl acetate-methanol). Found: C,56.26; H,6.58; N,16.62. $C_{15}H_{20}N_4O_2S$ requires: C,56.23; H,6.29; N,17.49%.

EXAMPLE 3

N-[4-[2-[[Methyl(4-amino-2-pyridyl)]amino]ethyl]phenyl]methanesulphonamide

A solution of the product of Preparation 2 (110 mg) in ethanol (10 ml) was hydrogenated at 20°C and 60 p.s.i. (4.1 bar) in the presence of 5% palladium on carbon (20 mg). The catalyst was filtered off and the filtrate was evaporated under vacuum to give a gum which crystallised on scratching. The solid was recrystallised from methanol to give the title compound (65 mg), m.p. 194-196°C. Found: C,56.60; H,6.32; N,17.40. $C_{15}H_{20}N_4O_2S$ requires: C,56.23; H,6.29; N,17.49%.

EXAMPLE 4

N-[4-[1-Hydroxy-2-[[methyl(4-amino-2-pyridyl)]amino]ethyl]phenyl]-methanesulphonamide

Hydrogenation of the product of Preparation 3 (100 mg) in ethanol (15 ml) according to the method of Example 3 gave the title compound (75 mg), m.p. 159-162°C. Found: C,52.59; H,5.97; N,15.90. $C_{15}H_{20}N_4O_3S$; 1/2 H_2O requires C,52.15; H,6.13; N,16.22%.

EXAMPLE 5

N-[4-[2-[[Methyl(1-methyl-2-imidazolyl)]amino]ethyl]phenyl]-methanesulphonamide

A solution of the product of Preparation 4 (0.44 g), and aminoacetaldehyde diethyl acetal (0.27 g) in pyridine (1.5 ml) was heated at 100°C for 5 hours and then evaporated under vacuum. The residue was dissolved in 2M hydrochloric acid (2.0 ml) and the resulting solution was heated under reflux for 1 hour and then cooled. It was next basified using saturated aqueous sodium bicarbonate solution and then the mixture was extracted several times with dichloromethane. The combined extracts were washed with water, dried (Na_2SO_4) and evaporated under vacuum to give an oil which was chromatographed on silica gel. Elution with a 30:1 mixture of dichloromethane and methanol followed by evaporation under vacuum of the appropriate fractions, gave the product (0.133 g), m.p. 117-118°C. Found: C,53.92; H,6.57; N,17.95. $C_{14}H_{20}N_4O_2S$ requires: C,54.52; H,6.54; N,18.17%.

EXAMPLE 6

N-[4-[2-[[Methyl(1,5-dimethyl-2-imidazolyl)]amino]ethyl]phenyl]-methanesulphonamide

A solution of the product of Preparation 4 (3.07 g) and propargylamine (2.04 g) in pyridine (18 ml) was heated at 100°C for 1 hour and then evaporated under vacuum. The residue was dissolved in dichloromethane and the solution was washed with saturated aqueous sodium bicarbonate solution, then water, and dried (Na_2SO_4). Evaporation under vacuum of the solvent gave an oil which was chromatographed on silica gel. Elution with a 19:1

mixture of dichloromethane and methanol, followed by evaporation under vacuum of the appropriate fractions, yielded an oil which crystallised on trituration with ether. Recrystallisation of the solid from ethyl acetate gave the product (0.525 g), m.p. 115.5-117°C. Found: C,55.57; H,6.93; N,16.99. $C_{15}H_{22}N_4O_2S$ requires: C,55.87; H,6.88; N,17.38%.

The following Preparations illustrate the source of the novel starting materials employed in the previous Examples:

PREPARATION 1

4-Amino-N-methyl-N-(4-pyridyl)benzeneethananine

(i) N-Methyl-N-(4-pyridyl)-4-nitrobenzeneacetamide

N,N'-dicyclohexylcarbodiimide (10.3 g) was added to a stirred solution of 4-nitrobenzeneacetic acid (9.0 g) in tetrahydrofuran (200 ml) at -15°C and the resulting solution was stirred at this temperature for 10 minutes. 4-Methylaminopyridine (6.8 g) was then added and the mixture was stirred at room temperature for 2 hours and then filtered. The filtrate was evaporated under vacuum and the residue dissolved in ethyl acetate. The solution was filtered, washed with saturated, aqueous sodium bicarbonate solution and then water, dried (Na_2SO_4) and evaporated under vacuum. The residual oil was chromatographed on silica gel using a methanol in ethyl acetate elution gradient (0-2%), and evaporation under vacuum of the appropriate fractions gave the product (3.0g) as an oil which crystallised on scratching, m.p. 71-73°C. The product was used directly in the next stage without further purification.

(ii) N-Methyl-N-(4-pyridyl)-4-nitrobenzeneethanamine

A solution of the previous product (2.50 g) in dry tetrahydrofuran (10 ml) was added over 5 minutes to a stirred 1.0 M solution of borane in tetrahydrofuran (40.0 ml) and the resulting solution was heated under reflux for 2 hours and then cooled. Excess 2M hydrochloric acid was added dropwise and the resulting solution was evaporated under vacuum. The residue was dissolved in water and the solution was basified with saturated aqueous sodium bicarbonate solution. This mixture was extracted several times with ether and the combined extracts were washed with water and dried (Na_2SO_4). Evaporation under vacuum of the ether solution gave a solid which was purified by chromatography on silica gel, using a 9:1 mixture of dichloromethane and methanol as eluent. Evaporation under vacuum of the appropriate fractions gave the product (1.35 g) as an oil which crystallised on scratching, m.p. 100-102°C (after recrystallisation from ethyl acetate-hexane). Found: C,65.26; H,5.92; N,16.18. $C_{14}H_{15}N_3O_2$ requires: C,65.35; H,5.88; N,16.33%.

(iii) 4-Amino-N-methyl-N-(4-pyridyl)benzeneethanamine

A solution of the product from (ii) (0.34 g) in ethanol (5 ml) was hydrogenated at 50°C and 60 p.s.i. (4.1 bar) in the presence of 10% palladium on carbon (25 mg). The catalyst was filtered off and the filtrate was evaporated under vacuum to give the product (0.28 g), m.p. 113-116°C.

PREPARATION 2

N-[4-[2-[[Methyl(4-nitro-2-pyridyl)]amino]ethyl]phenyl]methanesulphonamide

A solution of N-[4-[2-(methylamino)ethyl]phenyl]methanesulphonamide (0.57 g) (see EP 0281254) and 2-chloro-4-nitropyridine (0.39 g) in pyridine (20 ml) was heated under reflux for 6 hours and then evaporated under vacuum. The residue was dissolved in dichloromethane and the solution was washed with saturated, aqueous sodium bicarbonate solution and then dried (Na_2SO_4). Evaporation under vacuum of the solvent gave a solid which was chromatographed on silica gel. Elution with ethyl acetate, followed by evaporation under vacuum of the appropriate fractions, afforded the pure product as an orange solid (0.20 g), m.p. 180-182°C (after crystallisation from ethyl acetate). Found: C,51.47; H,5.23; N,15.79. $C_{15}H_{18}N_4O_4S$ requires: C,51.41; H,5.18; N,15.99%.

PREPARATION 3

N-[4-[1-Hydroxy-2-[[methyl(4-nitro-2-pyridyl)]amino]ethyl]phenyl]-methanesulphonamide

A solution of N-[4-[1-hydroxy-2-(methylamino)ethyl]phenyl]-methanesulphonamide (J. Med. Chem., 1966, 9, 88) (1.22 g) and 2-chloro-4-nitropyridine (0.79 g) in pyridine (50 ml) was heated under reflux for 4 hours and then evaporated under vacuum. A few ml of water were added to the residue and the mixture was extracted several times with dichloromethane. The combined extracts were washed with water, dried (Na_2SO_4) and evaporated under vacuum to give a gummy solid which was chromatographed on

silica gel. Elution with a 50:1 mixture of dichloromethane and methanol, followed by evaporation under vacuum of the appropriate fractions, gave the title compound (0.20 g), m.p. 200-202°C (after crystallisation from ethyl acetate-hexane). Found: C,49.08; H,4.89; N,15.23. $C_{15}H_{18}N_4O_5S$ requires: C,49.17; H,4.95; N,15.29%.

PREPARATION 4

(i) N,N'-Dimethyl-N-[2-(4-methanesulphonylamino)phenyl]ethyl-thiourea

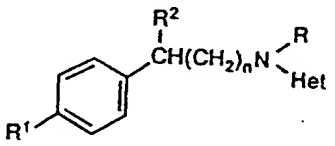
A solution of methyl isothiocyanate (0.28 g) in acetonitrile (10 ml) was added dropwise to a stirred solution of N-[4-[2-methylamino)ethyl]phenyl]methanesulphonamide (1.00 g) (see EP 0281254) in acetonitrile (16 ml) under reflux. The solution was heated further under reflux for 1 hour and then evaporated under vacuum. The residue was purified by chromatography on silica gel, using a 19:1 mixture of dichloromethane and methanol as eluent, to give a gum which, on trituration with a little ethanol, provided the product as a solid (0.80 g), m.p. 156-156.5°C (after crystallisation from ethanol). Found: C,47.77; H,6.41; N,13.85. $C_{12}H_{19}N_3O_2S$ requires: C,47.81; H,6.35; N,13.94%.

(ii) N,N'-Dimethyl-N-[2-[(4-methylsulphonylamino)phenyl]ethyl]-S-methylisothiouronium iodide

A solution of the previous product (0.30 g) and iodomethane (0.16 g) in ethanol (4 ml) was heated under gentle reflux for 15 hours and then evaporated under vacuum. The residue (0.44 g) was used directly in Examples 5 and 6.

CLAIMS

1. A compound of formula:



(I)

wherein R is C_1-C_4 alkyl;

R^1 is R^3SO_2NH or R^3CONH;

R^2 is H or OH;

R^3 is C_1-C_4 alkyl, C_3-C_7 cycloalkyl or NR^4R^5;

R^4 and R^5 are each independently selected from H and C_1-C_4 alkyl;

"Het" is either (a) 2-, 3- or 4-pyridyl optionally substituted by one or two substituents each independently selected from NH_2 and C_1-C_4 alkyl, or (b) 2-imidazolyl optionally substituted by one or two C_1-C_4 alkyl groups;

and n is 1, 2 or 3;

and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1 wherein R^1 is R^3SO_2NH; R^3 is C_1-C_4 alkyl or $NH(C_1$-C_4 alkyl); "Het" is either (a) 2- or 4-pyridyl optionally substituted by NH_2, or (b) 1-(C_1-C_4 alkyl)-2-imidazolyl optionally further substituted by a C_1-C_4 alkyl group; and n is 1.

3. A compound as claimed in claim 2 wherein R is methyl; R^1 is

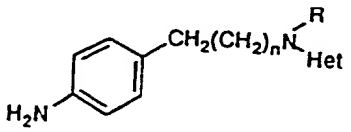
CH_3SO_2NH or CH_3NHSO_2NH; and "Het" is either (a) 4-amino-2-pyridyl or 4-pyridyl, or (b) 1-methyl-2-imidazolyl or 1,5-dimethyl-2-imidazolyl.

4. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3, together with a pharmaceutically acceptable diluent or carrier.

5. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3, for use in medicine.

6. The use of a compound of formula (I) or of a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3, for the manufacture of a medicament for the treatment of cardiac arrhythmias.

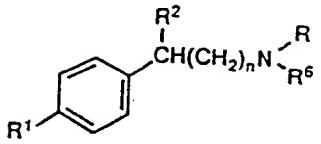
7. A compound of formula:



(II)

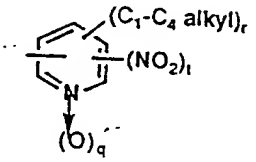
wherein "Het" is either (a) 2-, 3- or 4-pyridyl optionally subsituted by one or two C_1-C_4 alkyl groups, or (b) 1-(C_1-C_4 alkyl)-2-imidazolyl optionally further substituted by a C_1-C_4 alkyl group, and R and n are as defined in claim 1.

8. A compound of formula:



(III)

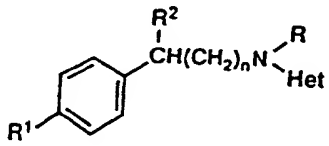
wherein R, R^1, R^2 and n are as defined in claim 1, and R^6 is either H or



wherein q is 0 or 1, r is 0 or 1, and t is 1 or 2, with the proviso that the sum of r and t is 1 or 2.

9. A method of treating or preventing cardiac arrhythmias in a human being which comprises administering to said human being an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 3, or of a pharmaceutical composition as claimed in claim 4.

10. A process for the preparation of a compound of formula:



(I)

wherein R is C_1-C_4 alkyl;

R^1 is R^3SO_2NH or R^3CONH;

R^2 is H;

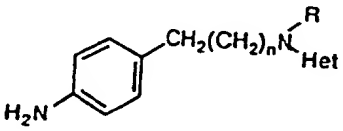
R^3 is C_1-C_4 alkyl, C_3-C_7 cycloalkyl or NR^4R^5;

R^4 and R^5 are each independently selected from H and C_1-C_4 alkyl;

"Het" is either (a) 2-, 3- or 4-pyridyl optionally substituted by one or two C_1-C_4 alkyl groups, or (b) 1-(C_1-C_4 alkyl)-2-imidazolyl optionally further substituted by a C_1-C_4 alkyl group;

and n is 1, 2 or 3;

and pharmaceutically acceptable salts thereof, which comprises reacting a compound of formula:



(II)

wherein R, "Het" and n are as previously defined in this claim, with, for a compound of formula (I) when R^1 is

a) R^3SO_2NH,

wherein R^3 is C_1-C_4 alkyl, C_3-C_7 cycloalkyl or NR^4R^5, wherein R^4 is H or C_1-C_4 alkyl and R^5 is C_1-C_4 alkyl, as appropriate, a sulphonyl halide of formula (C_1-C_4 alkyl or C_3-C_7 cycloalkyl)SO_2-(Cl or Br), a sulphonic anhydride of formula [(C_1-C_4 alkyl or C_3-C_7 cycloalkyl)SO_2]$_2O$ or a sulphamoyl chloride of formula $R^4R^5NSO_2Cl$, wherein R^4 is H or C_1-C_4 alkyl and R^5 is C_1-C_4 alkyl, in the presence of an acid acceptor;

b) H_2NSO_2NH,

sulphamide;

c) R^3CONH,

wherein R^3 is C_1-C_4 alkyl or C_3-C_7 cycloalkyl, either an acid halide of formula (C_1-C_4 alkyl or C_3-C_7 cycloalkyl)CO(Cl or Br) in the presence of an acid acceptor, or an acid anhydride of formula [(C_1-C_4 alkyl or C_3-C_7 cycloalkyl)CO]$_2O$;

d) H_2NCONH,

sodium or potassium cyanate under acidic conditions;

e) (C_1-C_4 alkyl)NHCONH,

a (C_1-C_4 alkyl)isocyanate; or

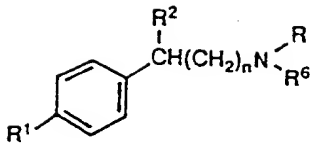
f) (C_1-C_4 alkyl)$_2$NCONH,

a carbamoyl chloride of formula (C_1-C_4 alkyl)$_2$NCOCl;
said process being optionally followed by conversion of the required product to a pharmaceutically acceptable salt.

11. A process as claimed in claim 10 wherein R^1 is R^3SO_2NH; R^3 is C_1-C_4 alkyl or NH(C_1-C_4 alkyl); "Het" is either (a) 2- or 4-pyridyl optionally substituted by one or two C_1-C_4 alkyl groups, or (b) 1-(C_1-C_4 alkyl)-2-imidazolyl substituted by a further C_1-C_4 alkyl group; and n is 1.

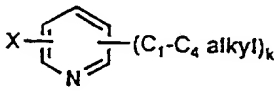
12. A process as claimed in claim 11 wherein R is methyl; R^1 is CH_3SO_2NH or CH_3NHSO_2NH; and "Het" is either (a) 4-pyridyl, or (b) 1-methyl-2-imidazolyl or 1,5-dimethyl-2-imidazolyl.

13. A process for the preparation of a compound of formula (I), wherein R^2 is H or OH; "Het" is 2- or 4-pyridyl optionally substituted by one or two C_1-C_4 alkyl groups; and R, R^1 and n are as defined in claim 10; and pharmaceutically acceptable salts thereof, which comprises reacting a compound of formula:



(III)

wherein R^6 is H and R, R^1, R^2 and n are as previously defined in this claim, with a halopyridine of formula:

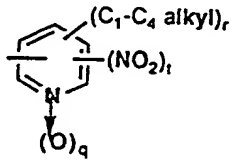


wherein X is 2- or 4-halo and k is 0, 1 or 2, said process being optionally followed by conversion of the required product to a pharmaceutically acceptable salt.

14. A process as claimed in claim 13 wherein R^1 is R^3SO_2NH; R^3 is C_1-C_4 alkyl or $NH(C_1$-C_4 alkyl); and n is 1.

15. A process as claimed in claim 14 wherein R is methyl; R^1 is CH_3SO_2NH or CH_3NHSO_2NH; and "Het" is 4-pyridyl.

16. A process for the preparation of a compound of formula (I), wherein R^2 is H or OH; "Het" is 2-, 3- or 4-pyridyl substituted by one NH_2 group and optionally further substituted by one NH_2 group or by one C_1-C_4 alkyl group; and R, R^1 and n are as defined in claim 10; and pharmaceutically acceptable salts thereof, which comprises reducing a compound of formula (III), wherein R^6 is



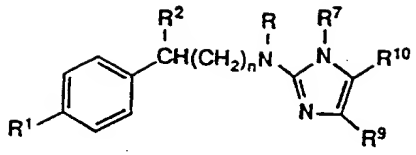
wherein q is 0 or 1, r is 0 or 1 and t is 1 or 2, with the proviso that the sum of r and t is 1 or 2, said process being optionally followed by conversion of the required product to a pharmaceutically acceptable salt.

17. A process as claimed in claim 16 wherein R^1 is R^3SO_2NH; R^3 is C_1-C_4 alkyl or $NH(C_1$-C_4 alkyl); and n is 1.

18. A process as claimed in claim 17 wherein R is methyl; R^1 is CH_3SO_2NH or CH_3NHSO_2NH; and "Het" is 4-amino-2-pyridyl.

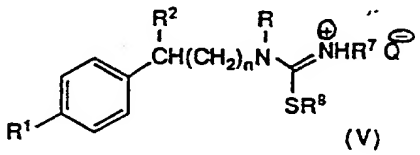
19. A process as claimed in any one of claims 16 to 18 in which the reduction is carried out by catalytic hydrogenation.

20. A process for the preparation of a compound of formula:



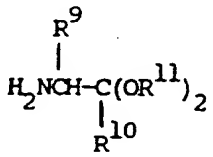
(IA)

wherein R^2 is H or OH; R^7, R^9 and R^{10} are each independently H or C_1-C_4 alkyl, with the proviso that not more than two of R^7, R^9 and R^{10} are C_1-C_4 alkyl; and R, R^1 and n are as defined in claim 10; and pharmaceutically acceptable salts thereof, which comprises reacting a compound of formula:



(V)

wherein R^7 is H or C_1-C_4 alkyl, R^8 is C_1-C_4 alkyl, Q is a leaving group and R, R^1, R^2 and n are as previously defined in this claim, with an acetal or ketal of formula:

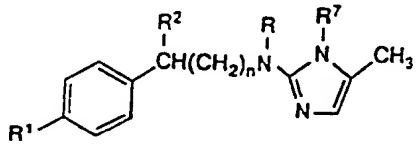


wherein either each R^{11} is C_1-C_4 alkyl or both R^{11} groups are joined to form a C_2-C_3 alkylene chain, and R^9 and R^{10} are as previously defined in this claim, to form an intermediate guanidine derivative, followed by hydrolysis thereof using aqueous acid, said process being optionally followed by conversion of the required product to a pharmaceutically acceptable salt.

21. A process as claimed in claim 20 wherein R^1 is R^3SO_2NH; R^3 is C_1-C_4 alkyl or $NH(C_1$-C_4 alkyl); and n is 1.

22. A process as claimed in claim 21 wherein R is methyl; R^1 is CH_3SO_2NH or CH_3NHSO_2NH; and R^7, R^9 and R^{10} are each independently H or methyl, with the proviso that not more than two of R^7, R^9 and R^{10} are methyl.

23. A process for the preparation of a compound of formula:



(IB)

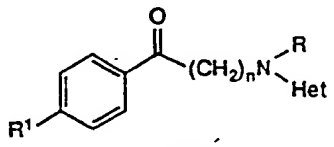
wherein R^2 is H or OH; R^7 is H or C_1-C_4 alkyl; and R, R^1 and n are as defined in claim 10; and pharmaceutically acceptable salts thereof, which comprises reacting a compound of formula (V) with propargylamine, said process being optionally followed by

conversion of the required product to a pharmaceutically acceptable salt.

24. A process as claimed in claim 23 wherein R^1 is R^3SO_2NH; R^3 is C_1-C_4 alkyl or NH(C_1-C_4 alkyl); and n is 1.

25. A process as claimed in claim 24 wherein R is methyl; R^1 is CH_3SO_2NH or CH_3NHSO_2NH; and R^7 is H or methyl.

26. A process for the preparation of a compound of formula (I), wherein R^2 is OH; "Het" is either (a) 2-, 3- or 4-pyridyl optionally substituted by one or two substituents each independently selected from NH_2 and C_1-C_4 alkyl, or (b) 2-imidazolyl optionally substituted by one or two C_1-C_4 alkyl groups; and R, R^1 and n are as defined in claim 10; and pharmaceutically acceptable salts thereof, which comprises reducing a compound of formula (VII):



(VII)

wherein R, R^1, "Het" and n are as previously defined in this claim, said process being optionally followed by conversion of the required product to a pharmaceutically acceptable salt.

27. A process as claimed in claim 26 wherein R^1 is R^3SO_2NH; R^3 is C_1-C_4 alkyl or NH(C_1-C_4 alkyl); "Het" is either (a) 2- or 4-pyridyl optionally substituted by one or two NH_2 groups, or (b) 1-(C_1-C_4 alkyl)-2-imidazolyl substituted by a further C_1-C_4 alkyl

group; and n is 1.

28. A process as claimed in claim 27 wherein R is methyl; R^1 is CH_3SO_2NH or CH_3NHSO_2NH; and "Het" is either (a) 4-amino-2-pyridyl or 4-pyridyl, or (b) 1-methyl-2-imidazolyl or 1,5-dimethyl-2-imidazolyl.

29. A process as claimed in any one of claims 26 to 28 in which the reducing agent is sodium borohydride.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01654

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 213/74 A 61 K 31/44 C 07 D 233/88
A 61 K 31/415

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 213/00 C 07 D 233/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0242173 (PFIZER) 21 October 1987, see page 10, lines 9-15	1,9,1
X		8
A	EP,A,0281254 (PFIZER) 7 September 1988, see page 23, lines 9-16 (cited in the application)	1,9,10
X		8
A	EP,A,0291210 (PFIZER) 17 November 1988	1,9,10
A	EP,A,0359389 (PFIZER) 21 March 1990	1,9,10

* Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
19-11-1991	17. 01. 92
International Searching Authority	**Signature of Authorized Officer**
EUR PEAN PATENT OFFICE	Mme Degmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [XX] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [XX] Claim numbers 9 because they relate to subject matter not required to be searched by this Authority, namely:

ALTHOUGH CLAIM 9 IS DIRECTED TO A METHOD OF TREATMENT OF (DIAGNOSTIC METHOD PRACTISED ON) THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9101654 SA 50567

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 14/01/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0242173	21-10-87	AU-B- 575745	04-08-88
		AU-A- 7144287	10-12-87
		JP-A- 62255474	07-11-87
		US-A- 4863948	05-09-89
		US-A- 4990509	05-02-91
EP-A- 0281254	07-09-88	AU-B- 586139	29-06-89
		JP-A- 63201167	19-08-88
		US-A- 4956382	11-09-90
		US-A- 5002547	26-03-91
		US-A- 5055473	08-10-91
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		US-A- 4835165	30-05-89
EP-A- 0359389	21-03-90	JP-A- 2083369	23-03-90
		US-A- 4968704	06-11-90
		US-A- 5057528	15-10-91